

Development of International Influenza Vaccine Production Capacity: Update of WHO Programme

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World Health Organization, Initiative for Vaccine Research (IVR)

Sustainable Influenza Vaccine Production Capacity

Stakeholders' Workshop

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Framework of the WHO programme

Objective:

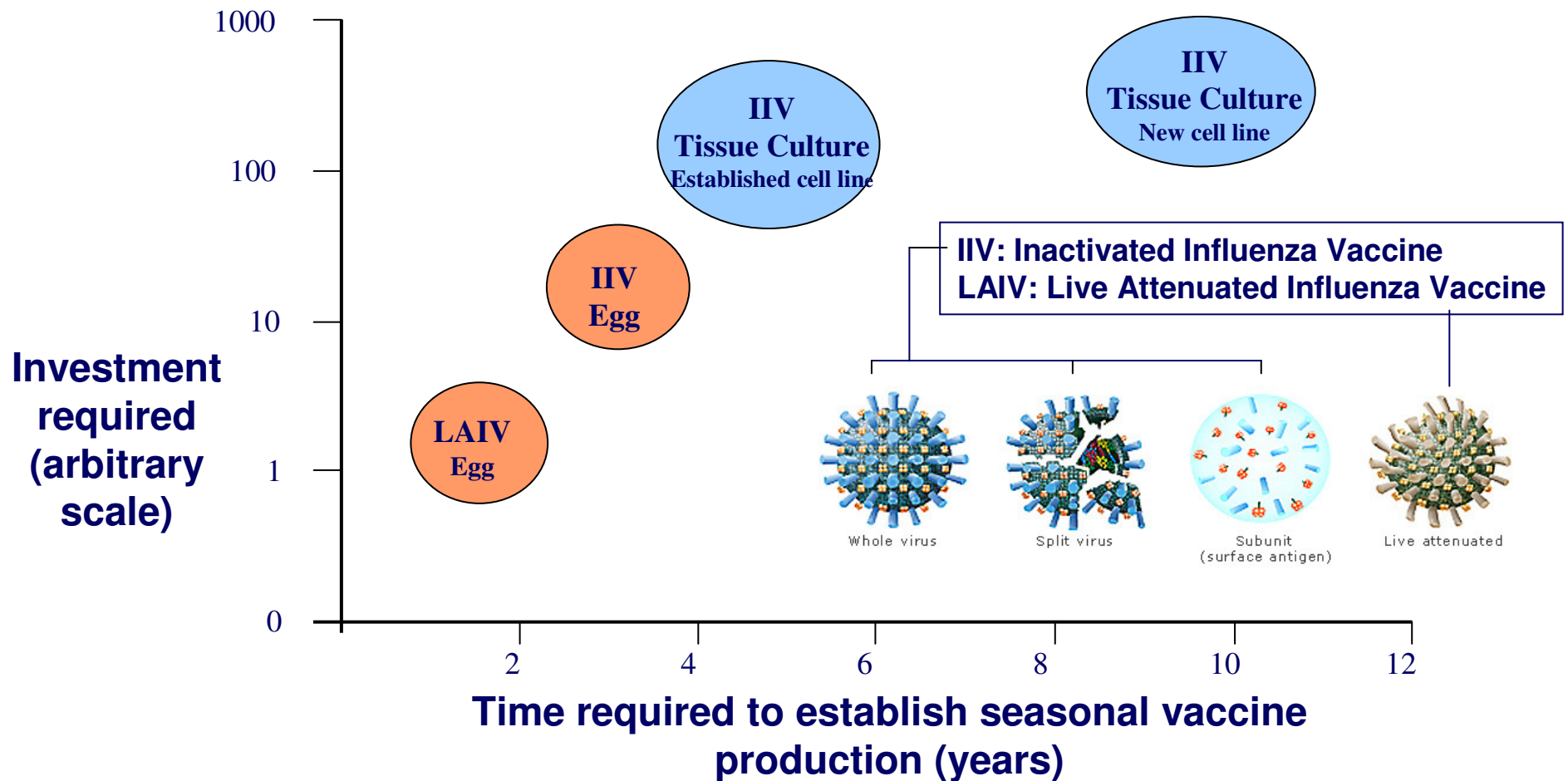
In the context of the **WHO Global Action Plan to increase supply of pandemic influenza vaccine (GAP)**, to facilitate acquisition of influenza vaccine production capacity in developing countries by supplying funds & facilitate technology transfer to eligible developing country producers

Financial support:

- US Department of Health & Human Services
- Government of Japan
- Asian Development Bank
- UK Government
- Government of Canada



Evaluation of Technologies available in the short/medium term: timeline and cost strategies



Two rounds of project initiation since the GAP inception (2006)

2007

- Bio Farma, Indonesia
- Birmex, Mexico
- Instituto Butantan, Brazil
- IVAC, Viet Nam
- Governmental Pharmaceutical Organization (GPO), Thailand
- Serum Institute of India (SII), India

2009

- Cantacuzino Institute, Romania
- Green Cross Corporation, Korea
- Razi Institute, Iran
- Torlak, Serbia
- Vacsera, Egypt



Status of project with Fill/Finish approach: Bio Farma (Indonesia) and Birmex (Mexico)



Multi- purpose blending, filling and packaging facility

- Technology transfer, bulk importation, training by Biken (Japan)
- Seasonal vaccine was licensed in 2009.
- Current commercial production: 200,000 trivalent doses for haj pilgrims
- Second grant targets full bulk antigen product. Pandemic H1N1 lot for clinical trial was produced.



- Blending, filling & packaging facility
- Antigen produced by Sanofi Pasteur in Europe
- Second phase: local antigen production in a new Sanofi Pasteur plant to be built in Mexico
- Product specific equipment for QC laboratory installed
- Construction and engineering plans for blending facility completed, construction initiated



Status of projects with Full Production approach: Butantan (Brazil) and SII (India) - 1



- Adjuvanted egg-based inactivated whole/split virion H5N1 influenza vaccine
- A new pilot plant for producing H5N1 vaccine established
- Based on own large scale split seasonal vaccine technology, acquired through technology transfer facilitated by Sanofi Pasteur
- Initiation of a clinical trial of experimental H5N1 and H1N1 vaccines is imminent
- Egg-based technology: whole virion alum adjuvanted inactivated vaccine and LAIV pandemic vaccine
- Has obtained a sub-licence from WHO on the LAIV technology in June 2009
- Pandemic H1N1 LAIV vaccine has entered clinical trial
- Inactivated pandemic H1N1 candidate vaccine clinical trial is planned for January 2010
- Actual commercial production of seasonal vaccines will depend on business decision



Status of projects with Full Production approach: GPO (Thailand) and IVAC (Vietnam) - 2



- Egg-based technology: split inactivated seasonal and LAIV pandemic vaccine
- Projected in-country production is 2 M seasonal vaccine dose per annum
- Process for split trivalent seasonal vaccine developed
- Has obtained a sub-licence from WHO on the LAIV technology
- Clinical trial of H1N1 LAIV was initiated in December 2009
- Production in pilot facility, a larger plant is under construction
- Egg based whole virion vaccine technology with alum adjuvant
- Estimated production target: 500,000 doses seasonal vaccine per annum
- WHO financial support to establish small scale production facility with chicken farm for egg-supply
- Design permits a production increase up to 2.5-3 M doses per year with minimal additional investment
- Newly built production unit in validation phase





torlak

Institute of Virology, Vaccines and Sera
Belgrade, Serbia



Status of new projects with Production Improvement: Torlak (Serbia) and Cantacuzino (Romania)

- Torlak intends to re-establish influenza vaccine production in a new refurbished small scale unit
- Egg-based technology: whole virion vaccine
- The grant supports the design and construction of a new filling department + equipment purchase + staff training
- Tender for main equipment pieces was organized
- Offers from potential basic design contractors were received
- Cantacuzino is a small scale licensed national producer of egg based split influenza vaccine
- The grant targets production optimization, pre-clinical and clinical studies
- Pandemic H1N1 lots were produced, a clinical trial in adults was completed and the vaccine has received domestic market approval
- Children trial with pandemic H1N1 vaccine is imminent



Status of new projects with Full Production approach:



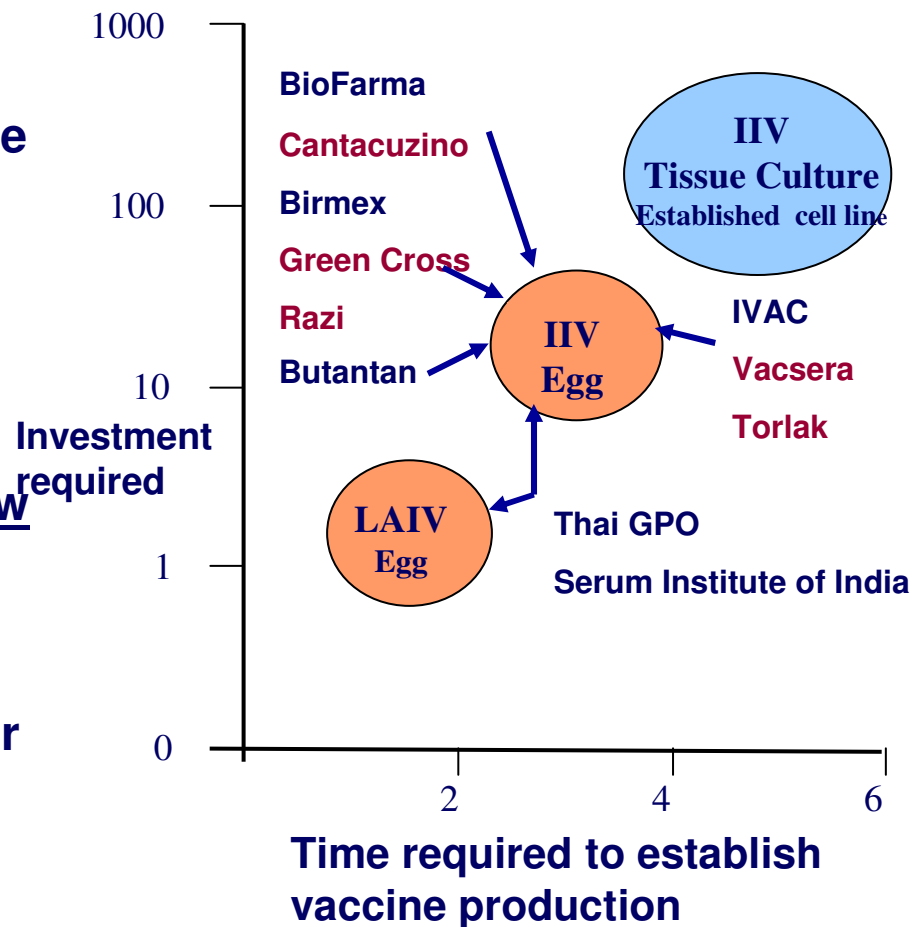
Razi Institute (Iran) and Vacsera (Egypt)

- The Razi Institute, an established producer of children's vaccines, intends to develop an egg based whole virion or split influenza vaccine approach in a small scale plant in Shiraz
- The grant targets equipment purchase and staff training
- Clean and dirty autoclaves for production area were purchased
- Collaboration on technology transfer under discussion with Netherlands Vaccine Institute
- Vacsera plans to build a new small scale production plant: 0.5-1.5 M seasonal doses per annum
- Egg-based whole virion or split vaccine
- In 2009 activity focused on conceptual design and site master plan
- Collaboration agreement on technology transfer with Netherlands Vaccine Institute is established

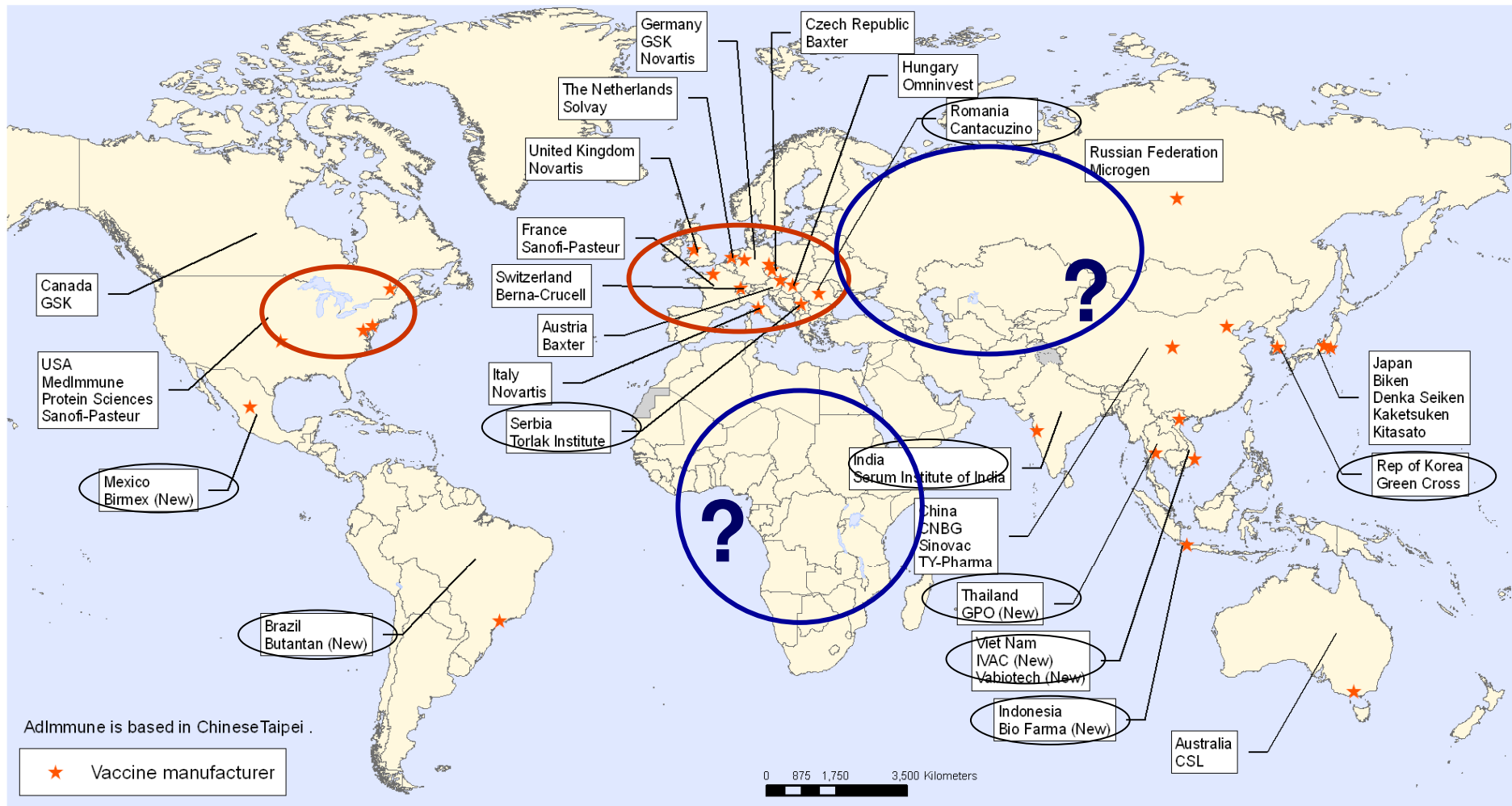


Status of new project with current seasonal vaccine producer: Green Cross Corporation (Korea)

- Green Cross is a large scale, recently licensed producer of egg-based split seasonal vaccine
- The grant targets the establishment of a dedicated pilot plant facility for H5N1 influenza vaccine production
- Alum adjuvanted whole virion H5N1 lots were produced, in view of clinical evaluation
- Non-adjuvanted, split (A)H1N1 vaccine was evaluated in phase I/II clinical trial and registered for use.



Map of current and new influenza vaccine manufacturers



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Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization

Provision of access to technology: the Russian LAIV

Institute of Experimental Medicine (IEM), St Petersburg, Russian Federation:
master donor strains (producing virus strains) and know how for the development and manufacture of live attenuated, seasonal and pandemic influenza vaccines.

Materials Transfer Agreement for virus strains



BioDiem

BioDiem, Ltd., Australia:

exclusive license in all countries of the world, excluding Russia and the Commonwealth of Independent States.



MERCK & CO., INC.
Whitehouse Station, N.J., U.S.A.

Nobilon The Netherlands:

exclusive license in certain geographical areas, including all Developing Countries.



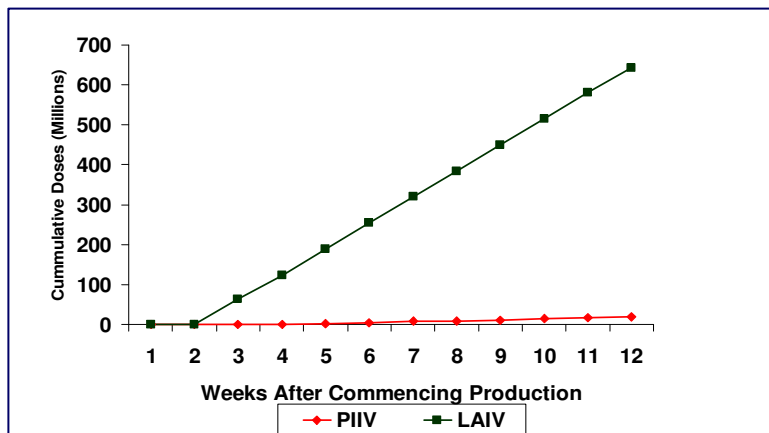
WHO

License to Know-how

- 1) non-exclusive license for egg-based vaccines in all Developing Countries, with the right to grant a sublicense to private companies or governmental or non-governmental organizations in developing countries
- 2) right to use the virus strains supplied by IEM.



Developing country vaccine manufacturer



The "Technology Hub" Concept

Major challenges encountered during Phase 1 of the programme

- Finding a technology provider proved very difficult
- Limited human resources at new manufacturer site



A possible solution: to create a "technology hub" to serve as technology provider

- **A technology platform** for transferring a robust production process with relevant documentation (SOPs, Batch Process Records, validation procedures, analytical methods and release criteria) > **established at the Netherlands Vaccine Institute**
- **A technology package** transferable to interested developing country vaccine manufacturers, upon request (and possibly against fees), without IPR hurdles
- **Selected technology:** Inactivated whole virion influenza vaccine produced in embryonated eggs



Achievements of the WHO Influenza Vaccine Programme: 2007-2009 – 1/2

- Financial and technical assistance with intense WHO monitoring was provided to **11 developing country manufacturers**:
 - Brazil
 - India
 - Indonesia
 - Serbia (new)
 - Mexico
 - Thailand
 - Vietnam
 - Romania (new)
 - Republic of Korea (new 2009)
 - Iran (new)
 - Egypt (new)
- **Six** of the 11 have produced **clinical lots of A(H1N1) vaccine**, four have completed or are conducting clinical trials of pandemic vaccine, two have registered this vaccine for use in humans.
- A royalty-free license was negotiated by WHO with Nobilon-Schering-Plough-Merck on the **LAIV technology**. A sublicense was provided to 3 developing country vaccine manufacturers (China, India, Thailand).



Achievements of the WHO Influenza Vaccine Programme: 2007-2009 – 2/2

- The **Technology transfer & training center** established at the NVI campus in Bilthoven, the Netherlands is fully operational.
- NVI through contractual agreements is engaged in bi-lateral technology transfer projects with developing country vaccine manufacturers (Vacsera, Egypt and IVAC, Vietnam - other agreements pending).
- *More information in Jan Hendriks' presentation*



Next steps

It will be essential

- to sustain both **technical and financial support for the new manufacturers** until registration of a product;
- to strengthen capacity of their respective **National - Regulatory Authorities**; and
- to initiate new projects in underserved regions, notably **sub-Saharan Africa and Eastern Europe**

Thank you!

Structural Diagram of the Influenza Virus

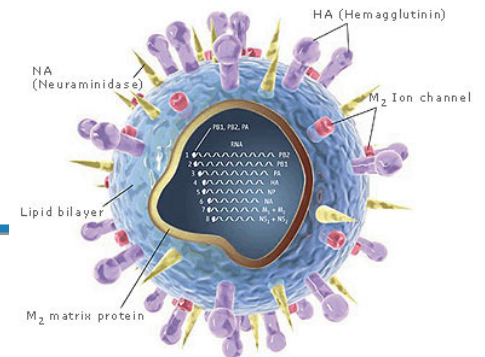


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